UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,890	12/29/2004	Briony Forbes	A20-073	9372

7590 02/26/2008

Henry D. Coleman
Coleman Sudol Sapone, P.C.
712 Colorado Avenue
Bridgeport, CT 06605

EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
02/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,890	FORBES, BRIONY	
	Examiner	Art Unit	
	CHRISTINA BORGEEST	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment and Arguments

Applicants' amendment filed 19 December 2007 is acknowledged. Claims 1-68 are cancelled. Claims 69-107 are new.

Objections/Rejections Withdrawn

Claim Objections

The objection to claim 67 because "(New)" is written twice as set forth at p. 2 of the previous Office action mailed 24 July 2007is withdrawn in response to Applicant's cancellation of that claim.

The objection to claim 68 because there is no period at the end of the claim as set forth at p. 2 of the previous Office action mailed 24 July 2007 is withdrawn in response to Applicant's cancellation of that claim.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 37-39, 42-68 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as set forth at p. 3 of the previous Office action mailed 24 July 2007 is withdrawn in response to Applicant's cancellation of claims 37-39 and 42-68. In addition, this issue is resolved because the new claims do not recite "able to effect binding of," but rather, "able to bind."

The rejection of claims 37-39, 42-68 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as set forth at p. 3 of the previous Office action mailed 24 July 2007 is withdrawn in response to Applicant's cancellation of claims 37-39 and 42-68. In addition, this issue is resolved because the new claims do not recite "on contact with an extracellular matrix (ECM)."

Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement

The rejection of claims 42-47, 67 and 68 under 35 U.S.C. 112, first paragraph, for scope of enablement as set forth at pages 4-7 of the previous Office action mailed 24 July 2007 is withdrawn in response to Applicant's cancellation of claims 42-47, 67 and 68. Nevertheless, the new claims raise the same issues of concern for the Examiner as outlined in the previous Office action, thus the rejection is reiterated below with respect to the new claims.

The rejection of claims 37-39 and 58-66 under 35 U.S.C. 112, first paragraph, for scope of enablement as set forth at pages 7-11 of the previous Office action mailed 24 July 2007 is withdrawn in response to Applicant's cancellation of claims 37-39 and 58-66. Nevertheless, the new claims raise the same issues of concern for the Examiner as outlined in the previous Office action, thus the rejection is reiterated below with respect to the new claims.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The rejection of claims 42-57, 67 and 68 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as set forth at pages 11-13 of the previous Office action mailed 24 July 2007 is withdrawn in response to Applicant's cancellation of claims 42-57, 67 and 68. Nevertheless, the new claims raise the same issues of concern for the Examiner as outlined in the previous Office action, thus the rejection is reiterated below with respect to the new claims.

New Rejections/Rejections Maintained

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 69-80 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims recite "a human IGFBP-2 molecule", which encompasses a product of nature. Note that this rejection could be overcome by including the phrase "isolated" or "altered", or some other such similar term, which is supported by the instant specification as filed, that indicates the hand of man.

Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69, 70, 71, 72, 74, 75, 76, 77, 78, 79, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106 and 107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an altered human IGFBP-2 able to bind IGF-I or IGF-II with high affinity wherein an inhibited release of IGF occurs on contact of said altered human IGFBP-2 molecule with an extracellular matrix (ECM), wherein said altered IGFBP-2 is the double mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170) as shown in Tables 2 and 3 (p. 20-21, respectively) of the specification and the isolated nucleic acid molecules encoding said altered IGFBP-2s, does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This rejection is similar to the one set forth at pages 4-7 of the previous Office action mailed 24 July 2007.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level

of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The prior art is silent with respect to these mutations with the recited activity limitations and thus unpredictable, so one of ordinary skill in the art must rely upon the amount of direction given by the inventor and the existence of working examples for guidance. The specification teaches only altered human IGFBP-2 molecule with an extracellular matrix (ECM), wherein said altered IGFBP-2 is the double IGFBP-2 mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170) (see Tables 2 and 3) were tested for the ability to bind IGF-I and IGF-II. The mutants introduced in the new claims, as recited in claims 74, 76, 77, 78, 102, 104, 105 and 106 have not been tested for their ability to bind IGF-I and IGF-II, and thus it is not predictable that they would be useful in the methods of treatment contemplated in the specification. Furthermore, the single mutants, K180A and K181A (see claims 71-72 and 100, for instance), were found non-resistant to proteolysis (see the specification at p. 23), thus these mutants could not predictably increase binding of IGF upon contact with an extracellular matrix or exposure to a protease. In other words, it is not clear that these muteins of IGFBP-2 could predictably be useful in methods of treatment.

Although the instantly rejected claims are product claims, the specification encompasses treatment of cancer (see for example, paragraph [0001]) so predictability of their usefulness in treatment has to be evaluated. Furthermore, with respect to claims 69 and 97, for instance, the amended claims recite “at least one of positions 180,

181, 227, 234 and 237 of human IGFBP-2 has been replaced with a neutral or acidic amino acid." According to the website downloaded on 15 February, 2008 at 3:55:54pm: elmhurst.edu/~chm/vchembook/561aminostructure.html;, there are 17 neutral or acidic amino acids, which makes 85 different possible variations on the claimed IGFBP-2s, which would have to be tested for their ability to reduce IGF mediated proliferation of cancerous cells, the use contemplated the specification (see for instance, paragraph [0001]). With respect to claims 75 and 79, which depend from claim 69 and claims 101, 103 and 107, which depend from claim 97, these issues are also of concern, for although the dependent claims further recite particular substitutions and deletions, they also encompass numerous possible variations on the claimed IGFBP-2, thus encompass many inoperative embodiments. Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Because the specification contemplates the use of the IGFBP-2 in therapy, consideration must be given to the amount of experimentation that would go into testing the ability of all of

these IGFBP-2 as effective cancer drugs. Making and testing agents for their ability to treat cancer is not the same as merely testing their ability to bind to IGF-I or IGF-II in vitro, and would require a great deal of experimentation on the part of one of skill in the art.

As a general matter, and as outlined in the previous Office action mailed 24 July 2007, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. See p. 5, last paragraph through p. 6, 1st paragraph of the previous Office action mailed 24 July 2007 for reasons for the unpredictability of gleaning functional characteristics from structural characteristics of proteins. Finally, the claims are not limited only to the substitutions or deletions recited in the claims. Furthermore, the IGFBP-2 molecules of the claims encompass those with un-recited additions. For example, in claim 69, an IGFBP-2 molecule could have a substitution in a position other than those recited at positions 180, 181, 227, 234 and 237, and for these alterations, the specification has no support.

Due to the large quantity of experimentation necessary to generate the IGFBP-2 muteins recited in the claims and screen them for activity and ability to treat certain cancers, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working

examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 81-84, 87, 89, and 93-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing IGF-mediated proliferation in MCF-7 cells, the method including the step of contacting said cells with the IGFBP-2 double mutant K180A K181A or the IGFBP-2 single mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170) or alternatively, a method of reducing IGF-mediated proliferation in HT29, CaCo and T84 cells, the method including the step of contacting said cells with the IGFBP-2 deletion mutant Des(114-170), does not reasonably provide enablement for the methods as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is similar to the one made over claims 37-39 and 58-66 in the previous Office action mailed 24 July 2007.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors

include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The art concerning the treatment of cancer with IGFBP-2 is extremely complex and unpredictable. The preponderance of the literature teaches that IGFBP-2 is associated with an increased cell proliferation in cancer cell lines (see Eiseman et al., Clin Cancer Res. 2007; 13: 2121-2127, p. 2121, right column, 1st paragraph—cited in previous Office action). In addition, increased levels of IGFBP-2 are found in prostate, Wilm's and CNS tumors (see p. 815, left column, last paragraph through entire right column in Rajaram et al., Endocr Rev 1997;18: 801-31, p. 815, left column, last paragraph—both cited in previous office action). Notably, it is taught that elevation of IGFBP-2 in patients with CNS tumors may be due to production of IGFBP-2 by the tumor itself (see Rajaram et al., p. 815, right column, last paragraph—cited in previous Office action), thus this does not support enablement for the claimed methods in any population of cells. Boulle et al. (J Clin Endocrinol Metab 1998; 83: 1713-20—cited in previous Office action) teach that "IGFBP-2 may be a regulator of the proliferative effects of IGF-II in [the adrenocortical] model" (see p. 1719, left column, last paragraph). Moore et al. (Int J Cancer. 2003: 105: 14-19—cited in previous Office action) teach that IGFBP-2 may play an active role in the progression of prostate cancer (see abstract; p. 18, right column, last paragraph), and suggest that a possible mechanism for this is the

"activation or inactivation of a regulatory switch" that leads to IGFBP-2 promoting carcinogenesis (p. 16, Figs. 2 & 3; p. 18, right column, last paragraph). Given the strong teaching in the literature that IGFBP-2 promotes cancerous growth in prostate cancer cells, this does not support enablement for reducing IGF mediated proliferation in prostate cancer by administration of the IGFBP-2 muteins of the instant invention. Regarding MCF-7 cells, Kibbey et al. (Mol Pharmacol 2006;69: 833-45—cited in previous Office action) teach that in spite of the reported proliferative role of IGFBP-2 in cancer cell lines, IGFBP-2 ameliorated cell growth in MCF-7 cells (see p. 838, right column, Figure 3), and further teach that "[the] lack of complete blockade of IGF-I action [by IGFBP-2] may be because of proteolysis of IGFBP-2 by proteinases expressed by MCF-7 cells (p. 833, left column, penultimate paragraph). Given the teaching in the literature regarding MCF-7 cells, the specification is enabling for a method of reducing IGF-mediated proliferation in MCF-7 cells, the method including the step of contacting said cells with the IGFBP-2 double mutant K180A K181A or the IGFBP-2 single mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170), but not to the methods as broadly claimed.

The claims encompass treatment of cancer, which is a difficult and complex problem. Testing the huge number of different IGFBP-2 muteins encompassed by the claims (see scope of enablement rejection immediately preceding this one) for the ability to treat cancer would require undue experimentation by one of ordinary skill in the art. Given the extreme unpredictability in the art with respect to the treatment of any cancerous cell population and the amount of experimentation that would require testing

all the encompassed IGFBP-2 muteins, one of ordinary skill in the art must turn to the specification for guidance. Regarding the treatment of cancer, the specification is silent. The specification teaches that of the five IGFBP-2 mutants tested (double mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170)), only the IGFBP-2 deletion mutant Des(114-170) showed any resistance to proteolysis and only in PC3, HT29, CaCo and T84 cells (see p. 22, Table 4 and 2nd paragraph of the specification and Figure 5). The other IGFBP-2 muteins (double mutant K180A K181A and the single mutants K227A, K234A, K237A) were tested in the T84 cell line, but none were found resistant to proteolysis (p. 23, 1st paragraph of the instant specification). According to Boulle et al., one of the possible mechanisms suggested for the increased proliferative effects of IGFBP-2 in the adrenocortical model is proteolysis (see p. 1718, right column, last paragraph to p. 1719, 1st paragraph):

> Proteolysis is another possible mechanism for regulating IGFBP-2/IGF-II interactions…IGFBP-2 proteolysis indeed occurred in adrenocortical tumor extracts, and large amounts of the IGFBP-2 proteolytic fragment were present in malignant tumors. By decreasing IGF-II affinity, IGFBP-2 proteolysis may increase IGF-II bioavailability and enhance its proliferative effects on adrenocortical tumor cells.

Given the teaching in the literature that proteolysis might be a mechanism for IGFBP-2 promotion of tumor growth, a showing in the specification that the Des(114-170) mutant was resistant to proteolysis in certain cell lines supports enablement for a method of reducing IGF-mediated proliferation in HT29, CaCo and T84 cells, the method including the step of contacting said cells with the IGFBP-2 deletion mutant Des(114-170), but not to the methods as broadly claimed.

Due to the large quantity of experimentation necessary to make and test all the encompassed IGFBP-2 muteins for the ability to reduce IGF mediated proliferation of cancerous cells and as effective cancer treatment agents, the lack of direction/guidance presented in the specification and the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art and the unpredictability of the art with respect to the role of IGFBP-2 in promoting cancer and the lack of evidence of its role in inhibition of cancerous cells (see the discussion above and the cited references), (the level of skill of those in the art), the unpredictability of the effects of mutation on protein structure and function (see previous scope of enablement with respect to breadth of the recited IGFBP-2 mutants, which is also directly relevant to the claimed methods), and the breadth of the claims which fail to recite adequate positive structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 85, 86, 88, 90, 91 and 92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is necessitated by amendment, as the newly amended claims now encompass specific mutations that either have not been shown to be effective in cancer treatment or have been shown to be non-resistant to

proteolysis (as in claims specifying treatment with the single mutants K180A and K181A).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

For the reasons outlined in the immediately preceding rejection, treatment of cancer is complex; the discussion above is applicable to claims 85, 86, 88, 90, 91 and 92. Although stated above, it bears repeating here that according to Boulle et al., one of the possible mechanisms suggested for the increased proliferative effects of IGFBP-2 in the adrenocortical model is proteolysis (see p. 1718, right column, last paragraph to p. 1719, 1st paragraph):

> Proteolysis is another possible mechanism for regulating IGFBP-2/IGF-II interactions…IGFBP-2 proteolysis indeed occurred in adrenocortical tumor extracts, and large amounts of the IGFBP-2 proteolytic fragment were present in malignant tumors. By decreasing IGF-II affinity, IGFBP-2 proteolysis may increase IGF-II bioavailability and enhance its proliferative effects on adrenocortical tumor cells.

Given the teaching in the literature that proteolysis might be a mechanism for IGFBP-2 promotion of tumor growth, a showing in the specification that the Des(114-170) mutant was resistant to proteolysis in certain cell lines supports enablement for a method of reducing IGF-mediated proliferation in HT29, CaCo and T84 cells, the method including the step of contacting said cells with the IGFBP-2 deletion mutant Des(114-170), but not for the mutants recited in claims 85, 86, 88, 90, 91 and 92. Furthermore, the single mutants, K180A and K181A, were found non-resistant to proteolysis (see the specification at p. 23), thus according to the teachings of Boulle et al., these mutants would not be effective in the treatment of cancer.

Due to the lack of direction/guidance presented in the specification and the absence of working examples directed to the ability of the claimed mutants to treat cancer (and the fact that some were shown to be non-resistant to proteolysis), the complex nature of the invention (cancer treatment), the contradictory state of the prior art and the unpredictability of the art with respect to the role of IGFBP-2 in promoting cancer and the lack of evidence of its role in inhibition of cancerous cells (see the discussion in the previous rejection and the cited references as well as the specific comment by Boulle et al.), (the level of skill of those in the art), undue experimentation would be required of the skilled artisan to use the claimed invention.

Response to Arguments regarding Enablement Rejections

Although the Applicant has submitted a new claim set, many of the arguments are relevant and will be addressed below.

The Examiner acknowledges that the Applicant has amended the claims to delete phrases "having an alteration" and "comprising a deletion", thus these issues have been resolved and are not addressed in the instant rejections (see p. 8, 1st paragraph of Applicant's arguments).

Applicant cites MPEP 2164.01 at p. 8, 3rd paragraph and argues that examples are not required for enablement and that a claimed genus can be enabled by a representative examples together with a statement applicable to the genus as a whole as long as one skilled in the art would expect the claimed genus to be used in that manner without undue experimentation.

This argument has been fully considered but is not found persuasive for the following reasons. First, in the instant case, the claimed methods encompass cancer treatment, and as explained in the preceding rejection, cancer treatment is a complex art and testing for the ability of an agent or protein to effectively treat cancer is not a routine matter (as would say, testing for the ability of a protein to bind to a receptor). Furthermore, as noted above, only certain muteins of IGFBP-2, namely the double IGFBP-2 mutant K180A K181A or the single IGFBP-2 mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170) showed any resistance to proteolysis. According to Boulle et al. (cited above), proteolysis of IGFBP-2, is part of the mechanism for proliferation of cancerous cells. Thus, the mutants shown incapable of resisting proteolysis (single mutants K180A and K181A) and/or those claims that encompass mutations that have not been tested for their ability to resist proteolysis and treat cancer do not make up "reasonable representative examples" to the genus as a whole, since one of skill in the art could not expect these to be used without undue

experimentation. In other words, the evidence presented in the specification is not commensurate in scope with the claims.

Applicant argues at p. 8, last paragraph to p. 9, 1st paragraph that the specification explains that human IGFBP-2 molecules wherein at least one of positions 180, 181, 227, 234 and 237 has been replace with a neutral or acidic amino acid is useful for reducing IGF mediate proliferation of cancerous cells.

This argument has been fully considered but is not found persuasive, because, in fact the specification provides evidence only that the double IGFBP-2 mutant K180A K181A or the single IGFBP-2 mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170) could be useful in the manner claimed by Applicant. This is more extensively explained in the Enablement rejections above.

Applicant argues at p. 9, 2nd paragraph that single mutants K180 and K181 (the argument does not specify the amino acid that replaces the K) could be reasonably expected to result in reduced ECM binding and inhibited release of IGF-I and IGF-II.

This argument has been fully considered but is not found persuasive for the following reason. The method claims encompass cancer treatment and according to Boulle et al. (cited above), proteolysis of IGFBP-2 is part of the mechanism for proliferation of cancerous cells. Thus, the mutants shown incapable of resisting proteolysis (single mutants K180A and K181A), could not reasonably be expected to be useful in cancer treatments.

Applicant argues at p. 9, last paragraph to p. 10, 1st paragraph that HT-29 cells are routinely used as an assay system and as a model of colorectal cancer and present evidence in the form of Wilson and Browning, Thus, data showing the effect of IGFBP-2 molecules of the present invention on HT-29 cell proliferation demonstrate the efficacy of the claimed invention in inhibiting proliferation of cancer cells.

This argument has been fully considered but is not found persuasive for the following reasons. First, data showing the effect of a single IGFBP-2 molecule (in this

case the deletion mutant Des(114-170) to resist proteolysis in a single type of cancer cells (the colorectal cell line, HT-29) does not mean that it would be generally predictable of inhibiting proliferation of all cancer cells. Second, according to Applicant's own specification, only the IGFBP-2 deletion mutant Des(114-170) showed any resistance to proteolysis and only in PC3, HT29, CaCo and T84 cells (see p. 22, Table 4 and 2nd paragraph of the specification and Figure 5). The other IGFBP-2 muteins (double mutant K180A K181A and the single mutants K227A, K234A, K237A) were tested in the T84 cell line, but none were found resistant to proteolysis (p. 23, 1st paragraph of the instant specification), thus Applicant's own specification does not suggest the ability of any of the claimed IGFBP-2 mutants to be useful in cancer treatment.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69, 70, 71, 72, 74, 76, 77, 78, 97, 98, 99, 100, 102, 104, 105 and 106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of particular substitution and deletion mutants, however, there is no identification of any particular portion of the remaining IGFBP-2 structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the double IGFBP-2 mutant K180A K181A or the single IGFBP-2 mutants K227A, K234A, K237A or the IGFBP-2 deletion mutant Des(114-170) as shown in Tables 2 and 3 (p. 20-21, respectively), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description

requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated altered IGFBP-2 molecules described as the double mutant K180A K181A or the single mutants K227A, K234A, K237A or the deletion mutant Des(114-170) as shown in Tables 2 and 3 (p. 20-21, respectively), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Argument regarding Written Description Rejection

Applicant argues at p. 10, last 2 paragraphs to p. 11, 1st paragraph that the Federal Circuit has recently clarified the law regarding written description in Faulkner-Gunter Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006), in which it explains that the specification is written for a person skilled in the art and so it is not necessary to spell out every detail of the invention, only enough as is required to convince a person of skill in the art that the inventor possessed the invention and to enable the person to make and use the invention without undue experimentation and that neither the specification nor the claims need to recite the entire amino acid sequences of the claimed molecules in order to satisfy § 112. The instant claims recite human IGFBP-2 molecules having specific amino acid modifications, e.g., specific replacements and/or deletions,

particularly because human IGFBP-2 is known, and the specification sets forth relevant portions of the amino acid sequences of several embodiments.

Applicants' arguments have been fully considered but are not found persuasive for the following reasons. The claims are not limited only to the substitutions or deletions recited in the claims. Furthermore, the IGFBP-2 molecules of the claims encompass those with unrecited additions. For example, in claim 69, an IGFBP-2 molecule could have a substitution in a position other than those recited at positions 180, 181, 227, 234 and 237, and for these alterations, the specification has no support.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 8:00am - 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646